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REVIEW

Cryoablation for Carcinoma of the Prostate

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Percutaneous transperineal cryoablation of the prostate is now available in the armamentarium for treatment of prostate cancer. Technical advances in real-time transrectal imaging of the prostate and improvements in cryosurgical equipment have brought this modality into the limelight of available prostate cancer management. Cryosurgery can be offered to many patients with prostate cancer. However, the main indications for its use include primary treatment for localized disease, salvage therapy after failure of traditional methods, and relief of local symptoms. A historical background, description of the technique, and clinical experience at several medical centers including the University of California San Diego, Allegheny General Hospital, University of Texas M.D. Anderson Cancer Center, and Crittenton Hospital, are presented. © 1996 Wiley-Liss, Inc.

KEY WORDS: review, prostate cancer, cryosurgery, cryoablation

INTRODUCTION

The use of low temperature (subzero) modalities for medical treatment has a long history. The first recorded use dates back to ~2500 BC when the Egyptians applied cold packs on wounds to relieve pain. In England in the 1840s, Dr. James Arnott was the first physician to use cryotherapy for neuralgia and cancers [1]. He postulated that temperatures below −30°C would be needed to treat tumors, and he promoted the use of iced saline via direct application and hollow irrigating tubes. Further advances in cryotherapy were related to the development of liquified gases. In 1899, a New York dermatologist named White began using liquid oxygen at temperatures −180°C to treat oral and skin lesions [2]. During the early 1900s, with the introduction of ether and ethyl chloride sprays and solidified carbon dioxide, cryosurgery was primarily done by dermatologists. In 1938, the first closed cryosurgical device was devised by Fay, a neurosurgeon in Philadelphia [3].

The modern era of cryosurgery began following World War II when liquid nitrogen became available. In 1961, Cooper and Lee in the United States described the use of liquid nitrogen achieving cooling temperatures of −190°C in insulated probes attached to a circulating pump [4]. At this time, liquid nitrogen was commonly used for the treatment of various skin lesions, brain tumors, lesions of Parkinsonism, and other neuromuscular disorders. Currently available cryogens for medical use include freon-12 (−29.8°C), solidified CO^2 (−79°C), liquid nitrous oxide (−88.5°C), and liquid nitrogen (−195.8°C) [5]. Liquid nitrogen is most commonly used because of its availability and ease of storage.

The first urological uses of liquid nitrogen cryosurgery occurred in the mid-1960s by Gonder [6], who demonstrated that freezing produced adequate tissue destruction in the canine prostate. In 1966, Gonder and his associates [7] performed prostate cryosurgery in humans treating bladder outlet obstruction from both carcinoma and benign prostatic hyperplasia. The technique was accomplished transurethrally using a cryoprobe that was shaped like a urethral sound. Advantages ascribed to this technique included its rapid completion with the patient under a spinal anesthesia and minimal blood loss. Transurethral cryotherapy also provided effective local tumor control for patients who were poor open surgical candidates [8].

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Initial reports of metastases regressing after repeat prostate freezing raised the issue of an associated immunological mechanism, but this hypothesis has never been substantiated [9–11].

Complications of the transurethral technique of prostatic cryosurgery were so common and devastating at this time that urologists nearly abandoned this procedure. Urethral sloughing of necrotic tissue causing urinary obstruction requiring repeated manipulation, as well as fistulas, were very discouraging. Also, the monitoring of the procedure was imprecise employing mainly rectal palpation. Modifications of the procedure, includng perineal exposure to dissect off the rectum and monitoring by open cystostomy [12], still were insufficient to prevent cryodestruction of adjacent normal structures.

The procedure was modified in the late 1960s by Flocks, who used the open perineal exposure of the prostate, similar to perineal prostatectomy for placement of the cryoprobe directly into the malignancy [13]. In this fashion, the tumor was destroyed directly with less urethral sloughing. However, the control of the cryoablation was entirely visual and still inadequate. The most severe complication of urethral-rectal and urethral-cutaneous fistulas occurred in 12% of patients [13]. It must be understood that the full potential of this therapy was unrealized because the majority of patients treated by Flocks [13] and O'Donoghue [14] were those requiring palliation and local control of extensive lesions. Only a small number of patients had this treatment instead of standard radical prostatectomy or irradiation and thus comparison for efficacy could not be made.

Of interest were the results of open perineal cryosurgery as summarized in four published series [15–18]. Their results at 10 years follow-up showed that on a stage-by-stage basis, patients treated with open perineal cryosurgery had progression-free survival and overall survival rates equal to those treated with standard techniques. However, because at that time few urologists were interested in performing radical prostatectomy and the technique of perineal prostatectomy was confined to only a few centers, the utilization of open perineal cryosurgery never became particularly popular.

A further modification of the technique occurred in 1974 when Megalli used the closed perineal approach with a single percutaneous probe positioned and monitored via rectal palpation [19]. This modification avoided the open incision and resulted in less urethral sloughing. However, the placement of the probe and monitoring of the cryoablation were strictly by rectal palpation and empirical.

In the mid and late 1980s, two important breakthroughs in technological development, now very common to urologists, occurred that produced the current renewed interest in prostate cryosurgery. These advances include: (1) transrectal ultrasound monitoring of the prostate, and (2) improved percutaneous access to structures such as the kidney, liver, and prostate. In 1988, Onik [20] showed that real-time ultrasound was useful in monitoring prostate cryosurgery. Onik [21] also carried out a pilot study using transrectal ultrasound-guided cryoablation of the dog prostate revealing that precise probe positioning and accurate regulation of the freezing process could be achieved. He also described the ultrasound characteristics during cryoablation as a hyperechoic rim with anterior acoustic shadowing and the final destroyed prostate tissue as hypoechoic when compared to normal tissue [20]. Onik and his colleagues [22] then transferred this technique to the treatment of prostate carcinoma in humans. Their preliminary findings indicated that the technique improved the control of freezing, which in turn decreased local complications. The problem of urethral sloughing was decreased further with the use of an investigational intraoperative urethral warming device. The procedure could be completed reasonably quickly with the patient under regional or general anesthesia and was associated with minimal blood loss and a very brief hospitalization, generally overnight.

Since the senior author [23] had considerable experience with the open perineal approach for prostate cryosurgery, the transition to transperineal cryoablation using ultrasound guidance was relatively smooth and occurred at the University of California San Diego Medical Center in early 1993. Our technique and experiences are presented.

TABLE I. Cryoablation: Mechanisms of Action

1. Protein denaturation via dehydration.
2. Transfer of water from intracellular to extracellular space.
3. Rupture of cell membrane from ice crystal expansion.
4. Toxic concentrations of cellular constituents.
5. Thermal shock from rapid supercooling.
6. Slow thawing.
7. Vascular stasis.
8. Variable tissue and cellular responses to subzero temperatures.

MECHANISMS OF ACTION

The principles of cryosurgery, including mechanisms of cell injury and cell death, have been well studied [4,6,23]. Three key factors are involved in freezing injury: (1) direct mechanical shock, (2) osmotic shock, and (3) cellular hypoxia [3,23]. The various well-recognized mechanisms of action in cryotherapy are listed in Table I.

Cryosurgery can be defined as the in situ freezing and devitalization of tissues. The freezing process must be applied and precisely controlled to produce a predictable zone of necrosis that will destroy the target lesion as well as an appropriate margin of surrounding tissue. Zacarian [24] in 1973 studied an in vitro model of cold-induced cellular injury and showed two important concepts. He proved that cryotherapy is both time- and temperature-

dependent and that two freeze-thaw cycles were more damaging to cells than one cycle.

Since temperature is a measure of the kinetic energy of molecular motion, as cellular temperature is lowered, molecular processes are slowed and can be arrested. Using a rapid freeze and slow, spontaneous thaw technique, the two primary effects noted are direct and indirect cryodestruction. During the period of direct damage at temperatures below −15°C to −20°C, the tissue goes through both hypothermia and true freezing. Hypothermic effects are divided into two types: metabolic uncoupling and compromise of structural integrity. Freezing begins in the intra- and extracellular compartments and the microvascular network. At a temperature of −15°C, the majority of the extracellular environment is frozen, causing trapping of tissue and production of shearing forces that disrupt the cellular structure. This process is known as mechanical shock. As ice is formed of pure solid water by the exclusion of electrolytes and organic chemicals, the cells become exposed to an extremely hyperosmotic environment. This extracellular hyperosmotic fluid draws water out of the cell resulting in increased tissue ice content plus shrinkage of cells, which then further damages cell membranes and causes protein denaturation. This is known as osmotic shock.

The slow process of spontaneous thawing is also a damaging environment for cells. As ice melts, any remaining intact cells are then exposed to a relatively hypotonic environment. This water returns to within the remaining cells causing cellular bursting.

The delayed or indirect ablative effects of cryosurgery continue mostly due to destruction of the microvasculature resulting in tissue hypoxia and thrombosis. Zacarian [25] found at temperatures less than −20°C, venules were more susceptible to injury than arterioles. Freezing promotes stasis of blood, which leads to thrombosis and subsequent coagulative necrosis of tissue. This process includes local edema with activation of the inflammatory cascade. Finally, tissue macrophages invade to resorb the lesion. The histopathologic changes seen postcryotherapy are described in detail. Further information on the cryobiology related to this treatment is beyond the scope of this chapter, but interested readers are encouraged to pursue the writings of Gage [26].

INDICATIONS

At the University of California San Diego Medical Center, indications for prostate cryosurgery fall into three broad categories. The first and largest of the three groups is patients who have localized disease without prior treatment and who are either offered or elect to undergo this technique rather than radical prostatectomy or irradiation. These patients comprised the smaller group in the series by Flocks et al. [13]. The second category includes those patients who have had recurrent or relapsing local prostate cancer following radical prostatectomy, cryosurgery, or irradiation (external beam, brachytherapy, or a combination of the two). The third and smallest group of the three includes those patients who have large local lesions, often in the presence of metastatic disease, where the procedure is indicated for the control and prevention of local complications such as repeated hematuria, urinary obstruction, and retention. This group was the larger category of patients treated by the open perineal approach by Flocks et al. [13].

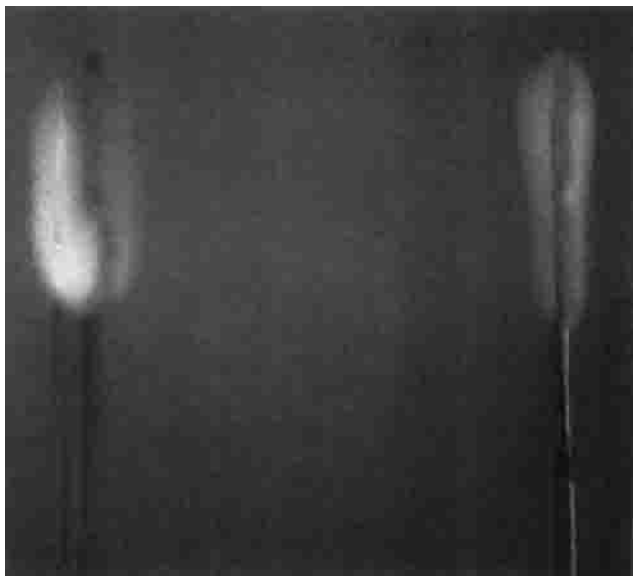

Fig. 1. Comparison of actual freeze zone achieved in water by the Accuprobe 450SP (left) and Cryotech LCS 3000 (right) cryoprobes.

CURRENT TECHNIQUES AND PATIENT FOLLOW-UP

The goal of prostate cryotherapy is the ablation of the entire gland and in some cases ablation of areas of local tumor extension. The procedure is performed using either the AccuProbe 450SP instrument from Cryomedical Sciences (Rockville, MD) or the Cryotech LCS 3000 device supplied by Candela Laser (Derbyshire, UK), both employing cryoprobes 3 mm in diameter. Kaplan [27] studied both cryoprobe systems and found the current technology provides precise, reproducible freeze boundaries and temperature control. Currently, most cryosurgeons use the AccuProbe system, and probe tip temperatures approaching −160°C are achieved. Figure 1 represents the actual freeze zone produced by the AccuProbe 450SP and Cryotech LCS 3000 probes. We use the Bruel and Kjaer transrectal ultrasound apparatus employing a 7.5 MHz transducer.

Preoperatively patients undergo digital rectal examination of the prostate, prostate biopsy, urinalysis, chest X-ray, standard bone radionuclide scan, and measurement

of complete blood count, chemistry panel, alkaline phosphatase level, prostate specific antigen (PSA) level, and prostatic acid phosphatase level. Pelvic magnetic resonance imaging and/or computerized tomography are performed on selected patients, looking either for extraprostatic extension or regional pelvic lymph node involvement. Patients with prostate glands measuring >40–50 grams are placed on preoperative endocrine therapy to reduce the volume, also known as downsizing. We have found up to 50% shrinkage in gland size in this fashion. Typically, endocrine therapy consists of luteinizing hormone-releasing hormone agonist (LHRH-agonist) and/or antiandrogen therapy for a minimum of 3 months.

Three freezing techniques are presented: single and double freeze-thaw cycles and pull-back freeze.

Single Freeze-Thaw Cycle

Patients receive perioperative antibiotics for dorsal lithotomy position and cystoscopy is performed to determine the local anatomy and pathology, and also to rule out any unrecognized lesions. A percutaneous suprapubic cystostomy catheter is inserted under cystoscopic guidance, and a 22 French Foley catheter is placed per urethra. If needed, the scrotum is sutured to the anterior abdominal wall to allow access to the perineum. Sterile saline warmed to 40°C is infused to irrigate the lower urinary tract with the inflow via the suprapubic tube and the outflow via the urethral catheter. This warm irrigation is employed to prevent urethral freezing and subsequent necrosis and stricture.

Ultrasound monitoring of the prostate is then carried out looking for asymmetry, overall dimensions, and evidence of extraprostatic extension. Five cryoprobes are used with the probe pattern of placement consisting of two probes anterolaterally, two posterolaterally, and one in a suburethral location (Fig. 2). Additional probes can be placed in an extraprostatic position such as in the seminal vesicles, should there be evidence of disease in that area. The key is to minimize the risk of urethral-rectal fistula, yet cover the entire prostate to its capsule by keeping a 1 cm margin from probe tip to capsule. Onik found that the positive postoperative biopsy rate was reduced from 37.5% when two cryoprobes were used to 14% when five probes were employed [22].

During the visualization via ultrasound, five 18-gauge needles are positioned percutaneously in the prostate down to the prostatovesical junction using a perineal biopsy guide. The stylets are withdrawn and replaced with a 0.038" J-tip guidewire, which is inserted through the needed. The needle can then be removed. All this is easily monitored by ultrasound. Small skin incisions are made into the perineal skin to allow the entry of the dilators and cannulas over the guidewires. After tract dilation is complete to the level of the prostatovesical junction, the guidewires and dilators are removed leaving

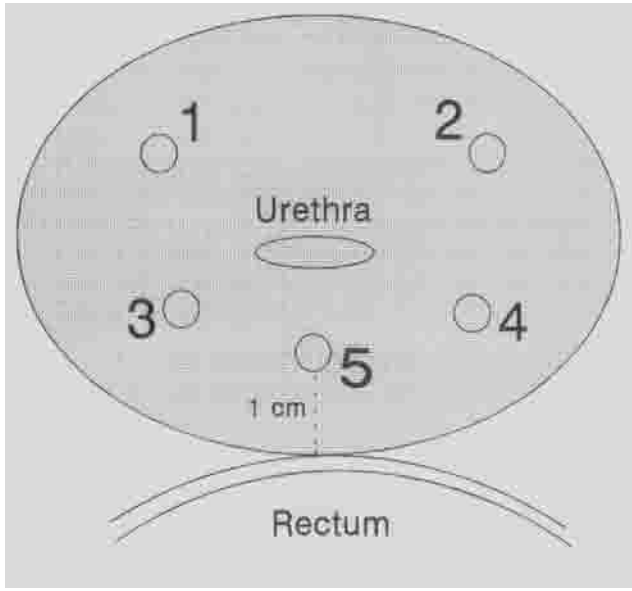

Fig. 2. Cryoprobe placement. Five probes used (1 and 2 are anterolateral, 3 and 4 are posterolateral, 5 is suburethral). Note 1 cm distance kept between rectum and probe 5.

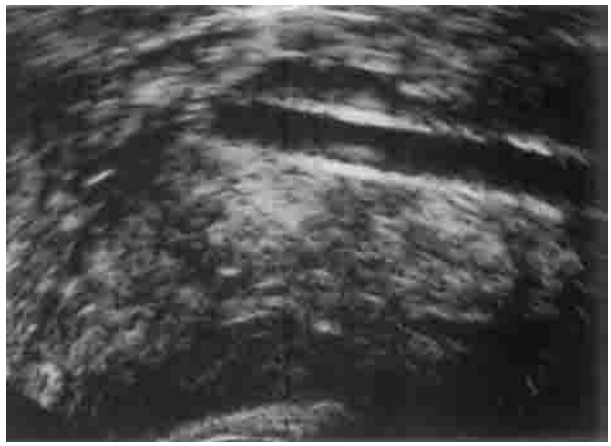

Fig. 3. Transrectal ultrasound longitudinal view of cannula in place prior to insertion of cryoprobe.

five cannulas in place (Fig. 3). The cryoprobes are inserted through the cannulas under ultrasound monitoring and the proximal insulating ends of the cannulas pulled back at least 2 cm over the cryoprobes exposing the working freezing element. Figure 4 represents a typical probe placement prior to initiating freezing. After verification of tip position, the probes are activated and fixed to the tissue at a temperature of −50–70°C. This "sticking" phase of the procedure occurs within 2 minutes.

Freezing is then carried out by quickly decreasing the probe temperature to approximately −196°C for 5–10 minutes; we use 5 minutes for the suburethral probe to decrease the risk of urethral-rectal fistula. The freezing is begun anteriorly to prevent the freeze zone from in-

Fig. 4. Transperineal cryoprobe placement prior to initiating flow of liquid nitrogen freezing.

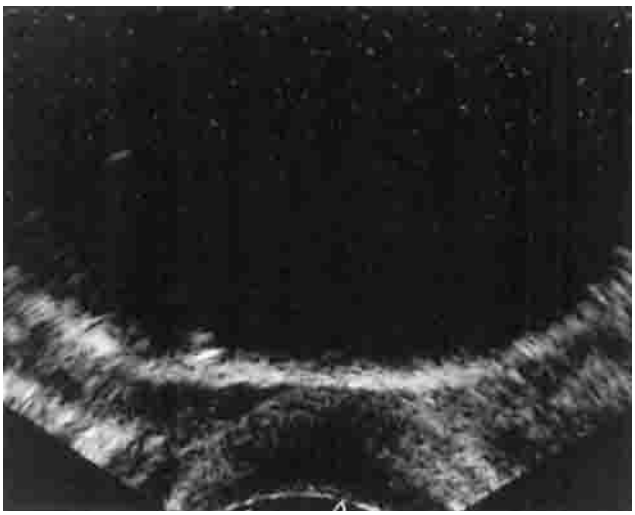

Fig. 5. Ice ball formation as visualized by transrectal ultrasound (transverse view).

terfering with the ultrasound imaging of the yet unfrozen gland. During the entire procedure, ultrasonic visualization continues to determine adequate ablation of the gland and tumor as well as to prevent injury to surrounding tissues such as the anterior rectal wall, bladder neck, and trigone unless the intent is to freeze beyond the prostate for local extension (Fig. 5).

After satisfactory cryoablation is accomplished, the cryoprobes are thawed slowly and withdrawn. We allow at least 5 minutes for probe thawing prior to removal, but the reconstitution of the image on ultrasound may take up to 20–30 minutes. The small perineal incisions are closed with interrupted 3-0 chromic suture, and the suprapubic and urethral catheters are irrigated and placed to straight drainage. We typically remove the urethral catheter in the recovery room or on postoperative day 1 when gross hematuria subsides.

Double Freeze-Thaw Cycle

As stated previously, there is evidence from the cryobiology literature that a repeat or double freeze-thaw cycle will provide more complete destruction should any cellular elements remain. Selected patients with larger tumors or glands >35–40 grams after preoperative endocrine therapy may be treated with this modification. In this technique, the cryoprobes are thawed slowly and when the prostate tissue image begins to reconstitute on ultrasound, the probes are kept in their initial position and reactivated similar to the first freeze. Total freeze time can reach 15 minutes. The second freeze-thaw cycle then proceeds with monitoring via transrectal ultrasound. In this fashion, theoretically, any surviving cancer cells will be freeze-sensitized and then forced to undergo an additional cycle of freezing [28].

Pull-Back Freeze

In larger prostate glands, the apex may not be ablated sufficiently with the initial placement of the five cryoprobes. To insure cryoablation of the apical area, after the cryoprobes are thawed and the prostate image reconstituted on ultrasound, the probes are visually repositioned in a more distal fashion. The tissue is fixed at −50–−70°C and another cycle of freeze-thaw occurs in that area.

Patient Follow-Up

During the first 24 hours postoperatively, the urethral catheter is removed and the patient is discharged home. Two weeks of oral antibiotics are prescribed. The patient is instructed to clamp his suprapubic cystostomy tube after ~1 week and begin voiding trials with measurement of residual urine volumes. When the postvoid residual volumes are <50–100 ml, the suprapubic cystostomy is removed. Patients are typically followed at 1, 3, and 6 months and at 6-month intervals thereafter. In addition to a full history of voiding habits and sexual function, digital rectal examination is performed along with urinalysis and prostate specific antigen (PSA) determinations. Cryoablation, like any other manipulation of the prostate, raises the serum PSA immediately postoperatively. We recommend waiting 4–6 weeks before obtaining a baseline post-cryoablation PSA. Follow-up ultrasound-guided biopsy is recommended at between 3–6 months and then again at either 1–2 years. Patients who were placed on endocrine therapy prior to the cryoablation have this treatment stopped postoperatively.

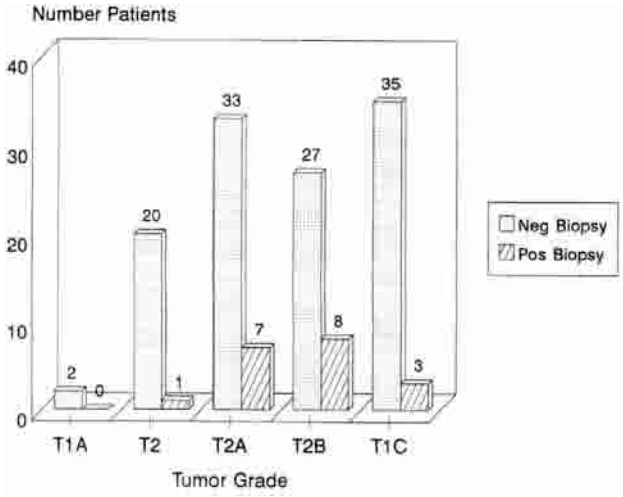

Fig. 6. Comparison of results of postcryotherapy biopsies to preoperative clinical stage in 136 patients followed for >6 months.

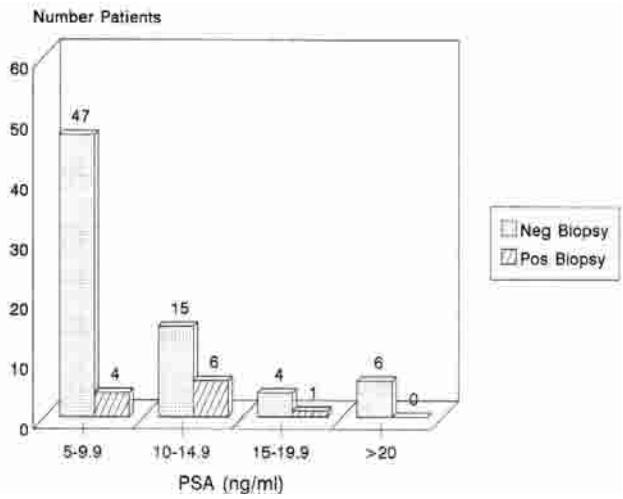

Fig. 7. Comparison of results of postcryotherapy biopsies to preoperative serum prostate specific antigen (PSA) levels in 83 patients followed for >6 months.

Re-treatment

As patients are followed postoperatively with both serum PSA and one or more biopsies, a cadre of patients will exist with evidence of persistence, if not recurrent, prostate carcinoma. Among other alternative therapies at that point, a second attempt at cryotherapy can be offered. The re-treatment technique is very similar to the initial treatment with the exception that the target (gland and tumor) is generally much smaller than at the time of the initial therapy and thus requires either fewer cryoprobes or a shorter duration of freezing. In the University of California San Diego Medical Center experience, re-treatment cryosurgery has been performed on 20 patients in a series of 292 men for a total re-treatment rate of 6.8%. Post-cryotherapy follow-up for patients who had re-treatment is similar to that for individuals who had only a single session of cryosurgery.

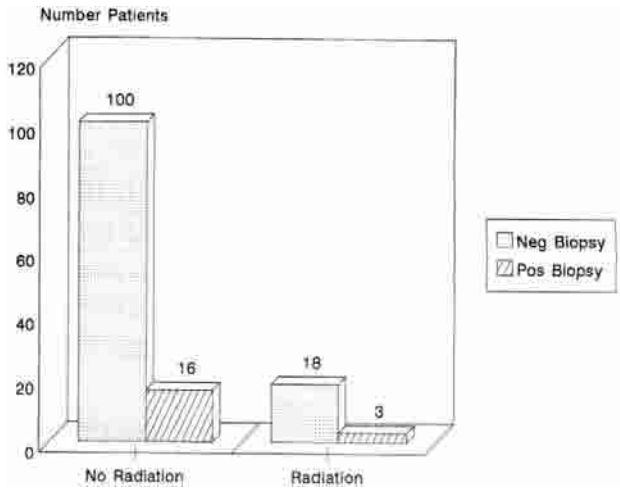

Fig. 8. Comparison of results of postcryotherapy biopsies to presence (21 patients) or absence (116 patients) of prior radiotherapy for prostate cancer followed for >6 months.

RESULTS

University of California San Diego

Since March 1993, 292 men with prostate cancer have received prostatic cryoablation with a total of 312 procedures. Their clinical stages have included T_1-T_4, N_0-N_1, M_0-M_1. Their average age has been 68 years. Cryoablation has been accomplished with five cryoprobes in 80% of men. Most men voided spontaneously with removal of their suprapubic cystoscopy tube by 10–14 days. Of the 136 men who had a follow-up biopsy, negative biopsies occurred in 117 (86%) and persistent cancer was documented as a positive biopsy in 19 (14%) (Fig. 6).

Typically, PSA levels rise initially, likely secondary to prostatic infarction, but fall subsequently. Normal range PSAs have occurred in 83% of patients (75 of 90 followed), and one-half of these are in the near non-detectable range of <0.5 ng/ml. Figure 7 compares the results of post-cryotherapy biopsies to the preoperative serum PSA levels in 83 patients. Thus far there seems to be no statistical difference relating the pretreatment PSA level to the biopsy outcome.

In a smaller group of 21 patients receiving prostate cryoablation for relapses to prior irradiation, postoperative biopsies have been negative in 18 (86%). PSAs have been in the normal range in 10 to 15 (67%) with 6 of the 10 (40% of the total) in the near non-detectable range. Figure 8 compares the results of post-cryosurgical biopsies in patients who have had prior radiotherapy (21 patients) to those who have not had irradiation (116 patients). The biopsy negative and positive rates are equal in both groups.

Of the patients having a re-treatment cryosurgery, one

has had a second post-cryosurgery biopsy and is now biopsy negative with a PSA of <0.2 ng/ml. In the entire series, no perioperative deaths have occurred and no patients have required transfusion.

Allegheny General Hospital

As stated earlier, the first use of transperineal cryoablation using ultrasound guidance for prostate cryosurgery was performed at the Allegheny General Hospital (Pittsburgh, PA) by Onik et al. [21]. Miller et al. [29] and Cohen [30] have recently updated results on 383 patients who had undergone 443 cryosurgical procedures. Clinical stages included 33 men with stage A_1, 41 with A_2, 45 with B_1, 75 with B_2, 100 with stage C, 30 with stage T_0, and 17 with stage D_1 disease. Of 354 men biopsied at 3 months, 53 (15%) were positive for persistent carcinoma. Positive biopsies at 3 months were seen in 11.3% of patients who had no prior therapy, in 18.3% of men who had received hormone therapy, in 27.3% of men having prior radiation, and in 26.7% of men having both radiation and hormone therapy before cryosurgery.

The results of biopsies were also compared to the initial clinical stage. Positive biopsies were seen at 3 months in 8.5% of stage A patients, in 8.9% of those with clinical stage B_1, in 14.7% of B_2 stage, and in 22% of men with stage C. Forty-one patients are now available with data at 2 years including biopsy. The overall biopsy negative rate is 85.4% with positive biopsies seen in 6 men or 14.6%. The subgroup of patients having had no prior therapy before cryosurgery represents 24 of the 41 and the positive biopsy rate at two years in this subgroup is 16.7%.

University of Texas M.D. Anderson Cancer Center

At the University of Texas, M.D. Anderson Cancer Center (Houston), prostate cryoablation has been performed for salvage only, i.e., after failure to prior radiation therapy, chemotherapy, hormonal therapy, or combination. Eighty-nine patients who failed prior radiotherapy only have been treated with salvage cryoablation. Von Eschenbach [31] reported that the median interval from the radiation to the appearance of a positive biopsy was 3.5 years. At the time of cryosurgery, more than half of the patients had biopsies showing Gleason scores 8 through 10. Forty-seven of the 89 patients underwent a single freeze-thaw cycle with the remaining 42 undergoing a double freeze-thaw cycle.

Sixty-seven patients have been monitored with biopsies at 6 months. Fifty-two (78%) of the biopsies have been negative. However, the biopsy negative rate was only 69% in those patients having the single freeze but increased to 92% in the 25 patients having the double freeze-thaw cycle. Most patients experienced a fall in PSA following cryotherapy. Overall, 25% of the patients have undetectable PSAs, the results being similar in both the single and double freeze groups. However, to date none of the patients undergoing a second freeze-thaw cycle have had a subsequent increase of PSA.

Crittenton Hospital (Rochester, MI)

The results of prostate cryotherapy have been recently reported by Bahn et al. [32] and Lee et al. [33]. These authors have treated patients with combined antiandrogen therapy usually consisting of an LHRH agonist and an antiandrogen for a minimum of 3 months prior to performing cryoablation. These authors reported residual cancer, i.e., positive biopsies, at 3 months in only 2 of 134 patients (1.5%) who were clincially stage T_2 or less pretreatment. At 1 year follow-up, the positive biopsy rate in 34 patients is 3.9% for an overall residual cancer rate of 3%.

In patients with clinical stage T_3, the positive biopsy rate at 3 months was 11.3%. The overall positive biopsy rate in their clinical stage T_3 group was 14.1% when followed for 1 year.

Bahn et al. [32] and Lee et al. [33] also pointed out that the postcryosurgery PSA levels were significantly lower in patients who had negative biopsies. They report PSA levels averaging 0.4 ng/ml at 1 year in patients with negative biopsies.

Others

Long et al. [34] recently reported on 84 cryoablation procedures in 80 patients with clinical stage T_1-T_3 prostate carcinoma. Of their last 50 procedures, they found undetectable PSA levels in 90% of men at 3–6 months. These authors report a 15% positive biopsy rate.

Long et al. [35] also have performed 23 cryosurgical procedures on 21 patients with prostate cancer who had relapsed after radiation. Thus far only 10 patients have been studied with postcryosurgical biopsies, and 3 of the 10 showed tumor. In each case, the positive biopsies were noted only in seminal vesicle tissue. Undetectable PSA levels have been reported in two-thirds of their patients at last follow-up.

Shinohara and Carroll [36] reported on 70 cryosurgical prostate procedures in 65 patients. Residual cancer was noted in 9 of 49 patients (18%) at 3 months. More recently, these authors changed their technique to include standard double freeze-thaw cycles as well as extensive freezing of the periprostatic and apical areas. Patients treated with this modification have had a reduction in positive biopsies to only 4% with nondetectable PSAs seen in 64%.

COMPLICATIONS

In the UCSD Medical Center series, 169 patients have been evaluated by Weider et al. [37] for complications (Table II). Note that over one-half of the patients reported no problems. The 34 patients reporting impotence represents approximately one-half of those patients who had

TABLE II. Complications of Prostate Cryosurgery

University of California San Diego Program	(169 patients)
None	91
Impotence	34
Incontinence	11
Bladder neck obstruction requiring surgery	7
Urethrorectal fistula	7
Urethral stricture	7
Hematuria	3
Thrombosis hemorrhoids	2
Urethritis	1
Epididymitis	1
Urinary tract infection	1
Penile numbness	1
Unknown	4

TABLE III. Prostate Cryotherapy: Histopathologic Findings

Stromal—	Fibrosis
	Hemosiderin pigment deposits
	Chronic inflammation
	Hyalinization
	Necrosis
	Hemorrhage
	Calcification
Epithelial—	Basal cell hyperplasia
	Squamous metaplasia
	Residual carcinoma

reasonably normal sexual function prior to the cryoablation. Thus far, complications requiring operative management have occurred in 6.3% of all patients treated. In the immediate postoperative interval, perineal ecchymosis, urinary stress or urge incontinence, and genital edema are seen but are almost always transient. The rate of significant complications including urinary incontinence, urethral stricture, bladder neck contracture, and rectourethral fistula is higher in the group of patients having had relapse of prostate cancer following prior radiotherapy.

A greater number of complications including persistent cancer requiring radical prostatectomy have been reported by Cox and Crawford [38] and Grampsas et al. [39]. However, these authors' series included many clinical stage T_3 patients and patients with carcinoma recurring postirradiation.

PATHOLOGIC CHANGES

Histologic findings following prostate cryosurgery were first reported by Hansen and Wanstrup in 1973 [40]. These authors reported on mostly early histologic findings stating that the epithelial elements seen on these biopsies represented the initial or precryosurgery morphology. Later, Petersen et al. in 1978 reported on postcryosurgery prostate biopsies emphasizing cancer recurrences but not other histologic changes [41].

More recently, Shabaik et al. [42] reported on 64 patients from the UCSD Medical Center series where biopsies were performed from 5 to 48 weeks following cryosurgery. The significant findings in the stroma and epithelial components are listed in Table III. The earliest and most frequent changes noted were stromal fibrosis, basal cell proliferation in regenerating acini, and the presence of hemosiderin granules in the stroma. Other histologic changes observed were squamous metaplasia, stromal hemorrhage, inflammation, necrosis, dystrophic calcification, and recurrent or residual carcinoma. Eight patients showed persistent carcinoma, and these recurrences correlated with higher initial grade and stage but did not correlate with baseline PSA levels. Significantly, 6 of the 8 (75%) positive postcryosurgery biopsies showed no evidence of the cryoablation background of the stroma and epithelium as was seen in the 56 patients (87.5%) with negative postcryosurgery biopsies. Shabaik reported that these postcryosurgery histologic changes were consistent and easily recognized [42].

CONCLUSIONS

Ultrasound-guided percutaneous transperineal prostate cryosurgery has many attractive features both to the patient and clinician. The procedure can be performed rapidly, usually in a period of 2 hours or less on an outpatient basis, has minimal blood loss, and with the patient under regional or general anesthesia. With greater experience in using the equipment and technique, urologists can treat all stages of prostate cancer with relatively low morbidity.

The results of this technique in the treatment of prostate cancer appear promising. With the short-term follow-up available, it appears to be an effective modality for the eradication of localized cancer. Improved results in postcryosurgery PSA levels and negative biopsies may be available with modifications such as double freezing and pull-back freezing at the apex, although the complication rate also may increase with the increased destruction of tissue. Thus far, most complications that have occurred have been relatively minor and required limited intervention. With limited short-term follow-up from our series as well as other series, transrectal ultrasound-guided cryoablation of the prostate appears to be effective in controlling local prostate cancer with minimal morbidity.

Although longer follow-up is essential, prostate cryosurgery can be considered either as (1) primary treatment alternative to radical prostatectomy or irradiation, (2) salvage therapy for recurrent cancer following cryosurgery or irradiation, or (3) for debulking of large, symptomatic primary tumors.

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